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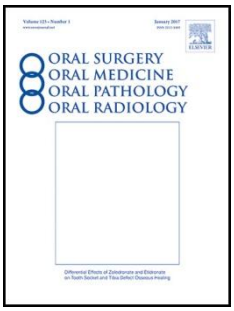

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Identifying criteria for diagnosis of post-traumatic pain and altered sensation of the maxillary and mandibular branches of the trigeminal nerve: a systematic review

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Clinical Relevance

There is a lack of high quality evidence on the diagnosis and management of iatrogenic injury to the trigeminal nerve, compounded by the absence of agreed standardized diagnostic tests and diagnostic criteria for nerve injury, associated altered sensation and pain.

Abstract

Objective: To systematically identify criteria used to diagnose patients with trigeminal nerve injury. Study design: A systematic review of the literature registered in the PROSPERO database. Inclusion criteria: patients diagnosed with nerve injury of the sensory divisions of the maxillary or mandibular branches of the trigeminal nerve, with reported tests and criteria used for diagnosis and persistent pain or unpleasant sensation associated with nerve injury. Results: 28 articles included. Diagnostic tests included clinical neurosensory tests (CNT) (89%), thermal quantitative sensory testing (25%), electromyography (7%) and patient interview (14%). Neuropathic pain was assessed using visual analogue scale (39%), use of neuropathic medication (7%), questionnaires including McGill and PainDETECT (21%). Functional impact was assessed in 14% and psychological impact in 7% of articles. Methodology in performing CNT, application of diagnostic terms and diagnostic grading of nerve injury was not consistent among the included articles making direct comparison of results difficult. Conclusion: Recommendations for assessment and diagnosis of trigeminal nerve injury have been made based on the best available evidence from the review. There is an urgent requirement for a consensus in diagnostic criteria, criteria for assessment and outcome reporting between stakeholder organisations in order to progress knowledge in this field.

Introduction

Iatrogenic injury to sensory branches of the trigeminal nerve is a known complication of oral and maxillofacial surgery.[1] Nerve injury can occur during many common surgical procedures including: local anaesthetic injection, mandibular third molar surgery, endodontic treatment, dental implant placement, bone grafting, orthognathic surgery, and fixation of facial fractures.[2] Injury to the trigeminal nerve can also occur as a consequence of systemic autoimmune conditions, bacterial and viral infections, and chemotherapy.[3,4] Injury to the maxillary and mandibular branches of the trigeminal nerve can result in altered sensation to the lips, skin of the cheek and chin, tongue, intraoral mucosa and teeth presenting as hypoaesthesia, paraesthesia, dysaesthesia, hyperalgesia and/or allodynia.[1,2,5] Severe injury to the lingual nerve can also alter taste perception.[1] Iatrogenic trigeminal nerve injury can have a significant functional impact on the patient with daily activities such as speech, eating, drinking, brushing the teeth, shaving, applying make-up and kissing causing discomfort or even pain.[6] This in turn can affect quality of life and psychological wellbeing.[7]

There is a lack of high quality evidence on the diagnosis and management of iatrogenic injury to the trigeminal nerve,[1] which is compounded by the absence of universally agreed diagnostic criteria for nerve injury and associated altered sensation and pain. In addition, the majority of published literature reports on the presence of sensory impairment without exploring the psychological burden and effect on quality of life which is often associated with permanent trigeminal nerve injury.[7] Currently there is no internationally agreed standardized set of diagnostic tests used in patients who present with trigeminal nerve injury. Most studies report the use of clinical neurosensory tests however the number of these tests used and the methods used to complete them vary widely in the reported literature.

The terminology for post traumatic sensory nerve injury with pain and or altered sensation in the trigeminal maxillary and mandibular divisions is also confusing and a matter of some debate. The terms Painful Post Traumatic Trigeminal Neuropathy (PPTTN)[8], Persistent dento-alveolar pain (PDAP)[9], and Chronic post-surgical pain[10] have all been used to describe post-traumatic nerve injury. The term neuritis is reserved for inflammatory processes causing temporary sensory alteration. This is excluded in this review as it is not persistent or post traumatic.

In order to advance knowledge in this field, consensus regarding diagnostic criteria and agreement on terminology used to define pain and altered sensation in relation to trigeminal nerve injury is required. The aim of this systematic review is, therefore, to systematically identify criteria that have been used to diagnose patients with trigeminal nerve injury. The criteria identified will be reported and used as a foundation to obtain a consensus on universally agreed diagnostic criteria for patients experiencing injury within the maxillary and mandibular branches of the trigeminal nerve.

Review questions:

1. What are the criteria used to diagnose post-traumatic neuropathy of the sensory branches of the maxillary and mandibular divisions of the trigeminal nerve?

2. What are the diagnostic criteria employed for persistent pain or unpleasant sensations following injury to the peripheral branches of the trigeminal nerve?

Methods

The full peer-reviewed search strategy and review protocol are available online in the PROSPERO database.[11] All types of study in English that include diagnostic criteria for post-traumatic neuropathy of the trigeminal nerve in human subjects were included. This comprised: randomized controlled trials (RCTs), controlled trials, cohort studies, cross-sectional studies, case series and case reports. Since post-traumatic nerve injury of the sensory branches of the trigeminal nerve is a relatively rare phenomenon, it was likely that there would be a lack of high quality research on this topic. Therefore, all types of study reporting on diagnostic criteria were included.

Search Methods for Identification of Studies

Databases

A search was initiated for each of the following electronic database to identify potential studies for inclusion in the systematic review:

- Medline via OVID (from 1966 to 2016)
- Embase via OVID (from 1980 to 2016)
- Psyc INFO American Psychological Association (from 1966 to 2016)
- CINAHL Cumulative Index to Nursing and Allied Health Literature (from 1966 to 2016)

Search Terms

The terms for sensory nerve injury used in the search included: neuropathy OR altered sensation OR paraesthesia OR anaesthesia OR dysaesthesia OR hyperalgesia OR allodynia, OR hypoaesthesia OR hyperaesthesia OR sensory disturbance OR neurosensory disturbance. These terms were combined with search terms for the maxillary and mandibular divisions of the trigeminal nerve (inferior dental nerve OR inferior alveolar nerve OR mandibular nerve OR trigeminal nerve OR lingual nerve OR infraorbital nerve OR inferior orbital nerve OR maxillary nerve OR mandibular nerve) and with search terms for injury (injury OR damage OR contusion OR section OR trauma OR lesion OR morbidity OR neurosensory deficit OR neuropathy) and diagnostic criteria (diagnosis OR evaluation OR assessment). The search was limited to articles in the English language. Terms were searched for in the title and abstract fields.

Hand Searching

Journals that were considered to be important to the field of research and therefore likely to contain relevant evidence were hand searched from 2010 onwards. These included: International Journal of Oral and Maxillofacial Surgery, Journal of Oral and Maxillofacial Surgery, British Journal of Oral and Maxillofacial Surgery, Journal of Dental Research, and Journal of the American Dental Association.

The references of papers that met the inclusion criteria and references from high quality review papers on the topic were also searched. The search was limited to articles published in the English language.

Inclusion/Exclusion criteria

Studies were included if:

- They contained data on patients diagnosed with nerve injury of the sensory divisions of the maxillary or mandibular branches of the trigeminal nerve.
- They reported the diagnostic tests and criteria used for diagnosis of nerve injury
- The sample also had a diagnosis of persistent pain or unpleasant sensations in the anatomical areas supplied by the trigeminal nerve in association with the nerve injury.

Studies were excluded if:

- They reported on laboratory or animal studies without human participants
- They reported on pain conditions which were not precipitated by trauma or viral/bacterial/autoimmune injury to the mandibular or maxillary divisions of the trigeminal nerve.
- They were not published in the English language
- They were conference abstracts or review articles which did not contain new research data

Outcome Measures

Primary Outcomes:

- A list of criteria used for diagnosis of post-traumatic neuropathy of the maxillary or mandibular branches of the trigeminal nerve
- A list of criteria used for diagnosis of persistent pain or unpleasant sensations following injury to the trigeminal nerve

Data Collection and Analysis

Selection of Studies

The title and abstract of articles obtained from the electronic database searches were assessed by two independent reviewers (MD and MH) to determine if the article met the inclusion criteria. For articles that appeared to meet the inclusion criteria or for which there was insufficient information in the title or abstract to make a clear decision, the full report was obtained. If there was disagreement between the two reviewers, consensus between these two reviewers was resolved by discussion. If agreement could not be reached, a third reviewer (TR) was consulted to assess the eligibility of the article. Following screening of titles and abstracts, the full text of each paper that appeared to meet the inclusion criteria were assessed by the two primary reviewers. All studies meeting the inclusion criteria underwent a validity assessment and data extraction.

The searches yielded 1231 results. These were screened using the selection criteria and those meeting the criteria were exported to bibliographic software (Endnote X7) for removal of duplicates. No additional results were obtained from hand searching of the relevant journals. Full texts of articles meeting the screening criteria were reviewed to determine if relevant information is present. If not present, the article was excluded and if present included (Fig. 1).

Data Extraction and Management

The data was extracted from each paper meeting inclusion criteria by the first reviewer and independently verified by the second reviewer. The data extracted from each included paper was added to a database by the first reviewer and checked for validity by the second reviewer.

For each paper, the following data was recorded:

- Year of publication, country of origin and the study design.
- Demographics of the participants including age and gender.
- The division of the trigeminal nerve that has been injured, the mechanism of injury, and the anatomical areas involved.
- The nerve injury characteristics including presence of anaesthesia, paraesthesia, dysaesthesia, allodynia, hyperalgesia or neuropathic pain.
- Diagnostic tests performed and their results
- Diagnostic criteria applied by the authors to define nerve injury
- Details about the management whether this was surgical, medical, or psychological intervention.

Synthesis of Results

Due to the heterogeneity of the results obtained and the aim of the review in identifying diagnostic criteria for nerve injury pain, it was not possible to combine results using a meta-analysis. A narrative report of the results is provided to aid further discussion and consensus on the application of diagnostic criteria to trigeminal nerve injuries and resulting symptoms.

Results

The results of applying the selection criteria are shown in Figure 1. A total of 28 articles were included and subject to data abstraction, which represented slightly over 2% of all identified citations via electronic search methodology.

Study characteristics

The study design and patient demographics are summarized in Table I. 57% (16/28) articles were retrospective case series, 29% (8/28) were prospective case series, 7% (2/28) were prospective randomized control studies, 4% (1/28) was a prospective cohort study, and 4% (1/28) a prospective case-controlled trial. The number of people in each article ranged from 5 to 478 patients. The gender distribution ranged from 16% to 85% female and mean age ranged from 25 to 49 years. Only 18% (5/28) studies assessed maxillary division neuropathy, most studies reported solely on mandibular branch neuropathy. The reported mechanism of injury ranged from multiple causes 50% (14/28) to specific procedures (orthognathic 18% (5/28), trauma 11% (3/28), local anaesthetic 7% (2/28), implants, third molar surgery and bone grafting 4% (1/28) each). 32% (9/28) reported on patients who had microsurgical repair of injured inferior alveolar and lingual nerves.[12-20] The other 68% (19/28) reported on the clinical characteristics and outcomes of patients presenting with injury of the

maxillary or mandibular branches of the trigeminal nerve. 14% (4/28) reported the use of medication to manage neuropathic symptoms.[16, 20-22] None of the authors reported the use of psychosocial approaches to pain management despite all included articles reporting on unpleasant or painful symptoms of neuropathy.

Articles reported a number of descriptors of altered sensation in their study populations (Table II), the most common being neuropathic pain in 86% (24/28) of articles, followed by anaesthesia in 54% (15/28), dysaesthesia in 43% (12/28), paraesthesia in 39% (11/28), allodynia in 36% (10/28), hypoaesthesia in 32% (9/28), hyperalgesia in 29% (8/28), hyperaesthesia in 18% (5/28) and hyperpathia in 7% (2/28).

Diagnostic tests for neuropathy (Table III)

Clinical neurosensory tests

Clinical neurosensory tests (light touch sensation, moving point direction, two-point discrimination, sharp –blunt discrimination, pinprick sensation, thermal sensation) were the most common reported diagnostic tests undertaken in 89% (25/28) of the included articles. The number of these tests carried out and the methods used and reported varied considerably between studies. All the above mentioned tests were carried out in 68% (19/28) of articles.[12-17,19,21,23-33] Light touch sensation was measured by Calabria et al[34] light touch and pinprick sensation by Jaaskelainen et al[35] and de Siquiera et al[36] and sharp-blunt sensation by Benoliel et al[8]. Patients were asked to complete the Ten Test – a self-reported measure of subjective function on the injured side by comparing touch sensation on the injured and uninjured sides and rating sensation on the injured side from 0-10 by Mundinger et al[18]. Neurosensory function was assessed by questionnaire in 2 studies[7, 37] and by patient self-reports only in one study[22]. The equipment used to carry out these tests varied between studies. Semmes Weinstein monofilaments or von Frey hairs were used to make a standardised measure of light touch sensation in 32% (9/28) of articles[12-16, 19, 21, 28, 36]; the other studies used cotton wool or did not report the method. Some studies reported the use of a pressure gauge to standardise the measurement of sharp and blunt sensation[16, 26] and one study reported using moderate digital pressure and vigorous rubbing of the neuropathic area to detect allodynia[8]. The use of camel hair for moving point testing was also reported[16, 19].

Thermal and electrical QST

Thermal quantitative sensory testing was reported in 25% (7/28) of articles[21, 26, 28, and 29,32,35,36]. The apparatus used for thermal QST varied between studies in relation to the number of stimuli applied, rate of heating and cooling and the size of the probe applied to the affected area. 43% (3/7) of articles reporting the use of thermal QST in their methodology did not state the size of probe applied[26, 29, 32] Two studies by the same authors reported using a specially constructed thermode of 18x6mm.[28, 35] In one of these articles, the size of the probe was changed to 9x9mm partway through the study period.[35] In the other article reporting thermal QST, a 5x5mm probe was used. In all studies a clinician trained in QST administered the testing.

Electrical detection thresholds were measured in three studies[8, 20, 21]. Three further studies tested the mental nerve blink reflex by application of an electrode to the centre of the mental nerve distribution and recording the responses of the orbicularis occuli muscles[27, 28, 35.]

Electromyography

Electromyography of the inferior alveolar nerve was used as a measure of nerve injury by two studies[28, 35]. The sensory action potential (SAP) was monitored using electrodes at the mandibular foramen and mental foramen fixed to a dental splint which delivered electrical stimuli. The amplitude and latency recorded were compared with laboratory reference values to determine the severity of injury.

Patient interview/self-report

Nerve injury was diagnosed using patient self-reported symptoms only in four studies[7, 18, 22, and 37]. This was measured using patient interview on consultation[7, 22], a number of psychological and quality of life questionnaires (detailed below) completed by the participant in the clinic[7], telephone consultation where the patient was requested to complete the Ten Test of subjective function (detailed above)[18] or a mailed questionnaire about symptoms of nerve injury[37] .

Diagnostic tests for neuropathic pain (Table III)

Patient interview/self-report

All of the included studies used patient self-reporting of the presence of pain over a period of time beyond normal post-surgical healing as a diagnostic criterion for the presence or absence of neuropathic pain.

Eleven studies recorded the intensity of pain experienced by using a visual analogue scale (VAS) where 0 indicated no pain and 10 the worst pain imaginable.[7,16,19,21-24,29-31,36,37] Nkenke used the VAS to measure "post-operative strain" to define the post-operative morbidity experienced by patients following surgery.[29]

Four studies explored the effect of neuropathic pain or dysaesthesia on daily function by interviewing patients about their ability to carry out specific tasks such as eating, drinking, applying make-up, kissing, shaving and tooth brushing despite the symptoms experienced.[7,30,31,37]

Two studies recorded the use of opioid or neuropathic medication by their patients as a measure of neuropathic pain intensity.[18, 22]

Questionnaires

Six studies used questionnaires to explore and categorise pain and discomfort experienced by patients, some validated and some based on the authors' own research. Benoliel et al used a "pain intake form" developed by the authors that included details about pain descriptors (patients chose one or more of the following pain descriptors: electrical, stabbing, throbbing, pressure, burning), pain duration, autonomic signs and interference with sleep.[21] D'Agostino et al also used their own questionnaire to record the type of discomfort, location and duration.[23] Gregg used the McGill Pain Questionnaire, where the patient chooses from a list of words to describe the character, frequency and intensity of their pain.[16] Elias et al and Smith et al used the PainDETECT questionnaire (PD-Q) to assess the presence of neuropathic pain.[7,24] Two studies used questionnaires to assess the

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psychological impact of pain.[7,26] Walter and Gregg used the Minnesota Multiphasic Personality Index (MMPI), Zung depression analysis and State Trait Anxiety Index to explore differences in the psychological status of patients with and without dysaesthesia.[26] Patients with dysaesthesia were found to have significantly elevated MMPI scores for hypochondriasis, depression and hysteria, and elevated Zung scores for depression. Smith et al used several questionnaires to measure the psychological impact of neuropathic pain including the Hospital Anxiety and Depression Scale (used to measure levels of depression and anxiety related to pain experienced), Pain Catastrophizing Scale (assessing response to pain stimuli and ability to handle the threat of pain), Pain self-efficacy questionnaire (measuring patients ability to carry on with normal daily activities despite pain) and Oral Health Impact Profile (a 14 item questionnaire measuring the individuals perception of the social impact of oral disorders on well-being and assesses discomfort, disability and dysfunction). [7]

Diagnostic LA blocks

Four studies reported the use of diagnostic local anaesthetic blocks to localise the involved nerve (inferior alveolar nerve, mental nerve, lingual nerve, or infraorbital nerve) when pain was the main complaint.[13-16]

Results / Outcome of diagnostic tests (Table IV).

Classification of Nerve Injury

The majority of included studies reported the outcome of clinical neurosensory tests and neuropathic symptoms experienced. 15 studies reported frequency of various neuropathic symptoms described in the IASP taxonomy (Table II): anaesthesia, hypoaesthesia, paraesthesia, dysaesthesia, neuropathic pain, anaesthesia dolorosa, hyperalgesia or hyperpathia.[16-21,25-31,35-37] Essick et al subcategorised the neuropathic symptoms into three groups: no alteration, negative (hypoaesthetic) sensations, active (paraesthetic or dysaesthetic) sensations, or mixed (negative + active) sensations.[25]

Two studies reported the sensory impairment level and divided patients into five groups, dependant on the results of clinical neurosensory tests.[32,33] Patients were classified as follows:

1. Normal: the responses on the injured side and the uninjured side exhibited comparable values that were within published normative limits at all three levels of testing.
2. Mild (level A test results (brush-stroke directional sensitivity and static two-point discrimination) were abnormal but normal in B (contact detection with Semmes Weinstein monofilaments) and C (pain threshold and tolerance using either an algometer, thermode, or sharp instrument).
3. Moderate (Level A and B test results were abnormal but normal in C)
4. Severe (Level A and B test results were abnormal and elevated in C)
5. Complete (Level A and B test results were abnormal and absent in C).

D'Agostino et al categorised the sensory function of the inferior alveolar nerve based on the Global Sensitivity Score: a sum of scores obtained from clinical neurosensory tests performed on each

patient out of a maximum score of 15. Sensory function was classified as normal (>12), subnormal (9-12), intermediate (6-9) or reduced (<6).[23]

Four of the included studies used the Medical Research Council Scale (MRCS), developed initially to evaluate sensory nerve injuries to the upper extremity and hand.[38,39] This scale evaluates functional sensory recovery and has been used by these authors to evaluate sensory function in a reproducible and measurable manner at each review appointment using the results of a set of clinical neurosensory tests (Table V). A grade of S3 or above was considered "functional sensory recovery" of the injured nerve.[12-15]

Classification of neuropathic discomfort/pain

Only seven of the included studies reported specifically on neurogenic discomfort or pain associated with sensory neuropathy. D'Agostino et al classified patients discomfort on a 5-point scale from absent to severe depending on their VAS score.[23]

Mundinger et al classified pain according to patients' use of neuropathic or opioid medication.[18] They reported successful outcomes based on the fact that 100% of included patients discontinued use of medication following nerve repair surgery. Park et al reported the percentage reduction in pain intensity on a VAS following prescription of neuropathic pain medication (gabapentin or tricyclic antidepressant). [22]

Two studies reported the results of the PainDETECT questionnaire (PD-Q).[7,24] This was originally developed and validated in German for the diagnosis of neuropathic pain in patients with chronic lower back pain.

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One study proposed and evaluated criteria for post-traumatic neuropathy of the trigeminal nerve (Table VI), termed "peripheral painful traumatic trigeminal neuropathy" (PPTTN) by comparing a group of patients with PPTTN to patients with classic trigeminal neuralgia in terms of history, clinical features, results of clinical and quantitative neurosensory testing and pain characteristics.[8]

Although three studies included data on the psychological impact of neuropathy on the included patients as described above[7,24,26], Smith et al reported specifically on the psychological burden on patients with neuropathic symptoms and pain.[7] Pain scores of $\geq$4 on an 11 point numerical reference scale were indicative of considerable daily suffering. Scores for anxiety, depression and quality of life based on the validated self-report questionnaires used in this study were used to classify the severity of neuropathy.

Discussion

The aim of this systematic review was firstly to systematically identify criteria that have been used to diagnose patients with trigeminal neuropathy and secondly to identify diagnostic criteria used to identify persistent pain or unpleasant sensations following injury to the peripheral branches of the trigeminal nerve. It is hoped that the criteria identified could be used as a foundation to develop standardized methodology for accessing such patients and obtain a consensus on universally agreed diagnostic criteria.

Diagnostic criteria for post-traumatic neuropathy

The majority of included studies (15/28) used the pain terminology defined in the International Association for the Study of Pain (IASP) taxonomy classification of chronic pain.[40] Although widely used, the application of these terms varies significantly between studies with terms such as paraesthesia frequently being used to cover all neuropathic symptoms. It is therefore difficult to make comparisons between studies. The application of these terms to trigeminal nerve injuries specifically has not been studied however they are the most frequently used and defined terms for neuropathy and chronic pain in the literature.

A variety of clinical neurosensory tests (CNTs) were used in 25/28 studies. These included mechanoreceptive tests; light touch sensation, two-point discrimination, brush directional stroke and nociceptive tests; sharp blunt discrimination, pinprick and thermal testing. A testing algorithm for the grading of trigeminal nerve injury was first described by Zungia and Essick in 1992 based on the results of several CNTs:

- Level A (brush stroke direction and static 2 point discrimination)
- Level B (contact detection with Semmes Weinstein monofilaments)
- Level C (pain threshold and tolerance using an algometer, thermode or sharp instrument)

Based on these tests nerve injury was graded as mild, moderate, severe or complete.[42] This method of assessment was reported as thorough and reproducible however is time consuming therefore not used in studies by other authors. D'Agostino et al graded trigeminal nerve injury based on numerical scores obtained from a number of CNTs as normal, subnormal, intermediate or reduced.[23] Again although reproducible by the same authors this grading system has not been used in other studies therefore cannot allow comparison between studies.

The methods used for CNTs also varied widely between studies. In the assessment of light touch or contact detection, the majority of authors use a piece of cotton wool lightly applied to the skin of the affected area. This test is quick and easy to do with minimal equipment however the force applied will vary between examiners. The use of Semmes Weinstein monofilaments ensures a known reproducible force is applied. This method is measurable and reproducible and has been recommended as the most sensitive and useful CNT for the assessment of trigeminal nerve injury.[42] The requirement for additional equipment and the time involved in carrying out this test means that it is not used by all authors.

Comment [DM3]: This information is included in Table VII therefore removed from the text

Similarly the two point discrimination test can be standardized and measurable if carried out using calipers to determine the minimum distance the patient can differentiate between two points. Some authors however have found this test to add little information to the findings of the light touch test,[43]to be less sensitive[44] and show greater variability between measurements.[45] Additionally, the average two point discrimination threshold varies significantly in different areas of the facial skin, peri-oral and intraoral mucosa therefore authors must be specific about the area tested for each affected nerve distribution and ensure that the test can be repeated in a standardised manner at subsequent visits.[46]

Pain perception can be tested with the use of a sharp probe or needle applied to the test site however the pressure applied is variable between examiners. Some authors report the use of an instrument which applies a reproducible 15 gauge pressure which would allow results to be

standardised.[16,26] Sharp blunt discrimination is usually tested using a sharp end and blunt handle of a dental probe however again the force applied will vary between examiners.[42]

A review of the methods used in sensory testing of trigeminal nerve injuries recommends the use of Semmes Weinstein monofilaments only as a reliable and reproducible test for sensation in the affected nerve distribution, in combination with a record of the patient's subjective function using a visual analogue scale.[42]

Although CNTs were the most commonly reported method of assessing trigeminal nerve injuries, they have been shown to have low sensitivity and only moderate specificity.[47, 48] In contrast, thermal Quantitative Sensory Testing (QST) and neurophysiologic tests have been shown to have high sensitivity in diagnosing and grading inferior alveolar and lingual nerve injuries.[49] A study comparing CNTs to QST and neurophysiologic tests in patients with IAN and LN injuries found that CNTs revealed abnormal findings in 83% of patients and thermal QST and neurophysiologic tests were abnormal in 90% of the patients.[49] Thermal QST involves the use of a small thermode which is placed in the affected nerve distribution. The thermode is set at a baseline temperature and heats or cools to increasing intensities at random intervals. The use of this test gives numerical values which can be used in further statistical analysis.[49] It also gives numerical results which can be used to categorise patients into those with reduced sensation (hypoaesthesia, anaesthesia) or elevated responses to stimuli (hyperalgesia, allodynia). Thermal QST has also been reported to have good reproducibility when used intraorally to assess somatosensory function.[50, 51]However, this review found differences in the methodology used to perform thermal QST in the included articles, with variation in the size of probe used, anatomical location tested and testing protocol. There are documented topographical differences in thermal sensitivity in the orofacial region, with the tongue tip and lip vermillion being particularly sensitive to warm, cold and mechanical stimuli and a decrease in sensitivity when moving posterolaterally from the mouth.[51] It is therefore recommended that a control site is also tested where possible for comparison when assessing somatosensory function in the orofacial region.[52]

The IASP Special Interest Group on Orofacial Pain published a comprehensive review of somatosensory testing methods and recommended a standardised chairside screening protocol for somatosensory testing to include application of tactile stimuli (cotton swab), pin-prick (tooth-pick) and cold (spatula kept in ice water). The patient was asked to compare stimuli to the normal side as more (hypersensitive), less (hyposensitive) or equally sensitive (normosensitive).[52] Test-retest and interexaminer reliability was found to be good by a recent pilot study of the technique.[51] A more comprehensive protocol based on the German Research Network on Neuropathic Pain (DFNS) protocol for quantitative sensory testing was also proposed to allow comparable results to be obtained in different centres in order to advance knowledge in the field (Table VII).[53]

Diagnostic grading

Several grading systems are reported for the assessment of lingual and Inferior alveolar nerve injuries to grade the success of nerve repair surgery. However, the emphasis in the grading system is mainly on the presence or absence of sensation rather than defining degrees of altered sensation or neuropathic pain.[42]

Four of the included studies used the Medical Research Council Scale (Table V). The use of this grading system does give comparable and reproducible results but does not include a grading of neuropathic discomfort or neuropathic pain.

Comment [DM4]: This information has already been stated in the results section therefore the reader is referred back to Table V.

Only 7 of the included studies in this review reported on the presence of neuropathic pain or discomfort in patients with trigeminal nerve injury. The diagnostic criteria used for neuropathic pain were not widely reported and it was routinely described as either present or absent.

The IASP Special Interest Group on Neuropathic Pain (NeuPSIG) set out the definition of neuropathic pain as "pain caused by a lesion or disease of the somatosensory nervous system" in 2008.[54] This definition has been widely accepted, however, the proposed grading system of possible, probable, and definite neuropathic pain has not been widely adopted. A recent systematic review of neuropathic pain reported that only 56 of 220 clinical studies had used the grading system.[55] None of the 28 studies in this review included graded diagnostics. Finnerup et al proposed adjusting the order of the grading system to reflect clinical practice to take into account aspects of the patients' history, clinical examination and diagnostic tests (Figure 2).[55]

Comment [DM5]: This information is included in Figure 2 therefore has been deleted to avoid repetition.

The application of this grading system to patients with trigeminal nerve injury will most likely lead to a diagnosis of probable neuropathic pain. Clinical neurosensory testing is a critical part in determining whether pain is neuropathic and initiating appropriate treatment. However the use of further imaging studies of the injured nerve will depend on sociocultural and economic factors and is not consistent throughout the world. In many cases the clinical history and previous treatment the patient has undergone (such as removal of a mandibular third molar tooth) will confirm the diagnosis.

The most commonly used diagnostic criteria for neuropathic pain in the included studies was rating of pain severity on a visual analogue scale (VAS). The VAS is one of the most commonly used rating tools for pain intensity and has been shown to be easy to understand, require no verbal or reading skills and has high sensitivity.[56]However it can be difficult for some patients to use, such as those with learning disabilities, young children and elderly patients who find it difficult to describe their pain intensity.[57] It also requires clear vision and needs to be administered on paper or electronically, rather than verbally.[58] However, pain scoring in patients with sensory nerve injuries can be unreliable and is often complicated by patients presenting with mixed features of anaesthesia, altered sensation and neuropathic pain.

Comment [DM6]: This information has already been stated in the results section

The use of questionnaires as a tool for the diagnosis of neuropathic pain was reported in two of the included studies. The PainDETECT questionnaire has been used to screen patients with trigeminal nerve injuries for neuropathic pain (Elias et al). The authors encountered problems with ensuring that patients completed all sections of the questionnaire and found that the PD-Q had poor sensitivity in identifying neuropathic pain associated with trigeminal nerve injury.[24] This was in agreement with the findings of Ukwas et al who examined its use in patients with orofacial pain, finding that it had poor sensitivity and reproducibility.[59] Other neuropathic screening tools such as the modified S-LANSS (Leeds Assessment of Neuropathic Symptoms and Signs) for intraoral use have shown similar limitations and did not have adequate accuracy in detecting orofacial pain conditions.[60] Such screening tools may be useful particularly in low-resource settings however they should be used only as an adjunct to history taking to alert the clinician to the possibility of neuropathic pain and the need for further more detailed assessment.[55] These questionnaires should

be interpreted with caution as they may wrongly classify patients and many have been developed based on an older and less precise definition of neuropathic pain.[55]

The classic features of sensory nerve injury are reported in most studies including neuropathic pain, anaesthesia, allodynia and paraesthesia. Functional impact of nerve injury was only reported by one team in two studies. Only two studies applied psychological impact screening tools in the assessment of patients with neuropathy. The biopsychosocial model of pain describes the interaction between sensory, emotional, cognitive and behavioural aspects which influence a patient's experience of and ability to cope with pain.[61] It is well recognised that psychosocial factors such as anxiety, depression, distress, catastrophizing and social isolation are risk factors for the development of chronic pain.[62] Assessment of psychosocial factors has therefore been included in the diagnostic criteria for temporomandibular disorders (DC/TMD). The Axis II protocol includes screening and self-report tools assessing pain intensity, pain-related disability, psychological distress, jaw functional limitations, and parafunctional behaviours, and a pain drawing is used to assess locations of pain. The comprehensive evaluation includes more detailed assessment of jaw functional limitations, psychological distress, anxiety and presence of comorbid pain conditions.[63] The fact that the included studies in this review failed to evaluate Axis II in all but 2 studies is a significant issue as managing patients with neuropathic pain relies mainly upon psychological therapies and medical pain management. Surgical management of post-traumatic nerve injury has not been shown to reduce the incidence of neuropathic pain.[64] If the pain, functionality and psychological impact is not assessed the patient cannot be managed effectively and the long-term outcome is likely to be poor.

One included study field tested proposed novel diagnostic criteria for peripheral painful traumatic trigeminal neuropathy (PPTTN).[8] The proposed criteria can be used to identify patients with pain following a trigeminal nerve injury and broadly follows the IASP classification of possible, probable and definite neuropathic pain (Table VI). The criteria were successfully applied to 96% of the patients with post-traumatic neuropathy suggesting that although further studies may be warranted to refine and validate the criteria they provide a useful starting point for definition of PPTTN. Expansion of these criteria to include non-painful trigeminal neuropathies would result in more widely applicable criteria which could be applied to all post-traumatic trigeminal neuropathies.

Terminology

The terminology used in describing painful neuropathy following trigeminal nerve injury is highly variable. It has been reported in the literature under many different names including: post traumatic neuropathy,[65] trigeminal neuropathic pain,[66] trigeminal neuropathy,[67] painful trigeminal neuropathy,[68] persistent dentoalveolar pain[69] and painful traumatic trigeminal neuropathy.[70] The two latter conditions are recognised terminology recommended by the International association of pain (IASP) and International Cranial Headache Disorders (ICHD). In the majority of included studies in this review it was referred to only as neuropathic pain. Chronic pain following surgery has been widely reported in the medical literature and is known to be associated with a number of common procedures including thoracotomy, breast surgery, limb amputation and herniorraphy.[71] A commonly accepted term for this condition is chronic post-surgical pain (CPSP) which has been reported to be present in up to 40% of patients attending chronic pain clinics.[72] The incidence of this condition following surgery has been reported in between 10-50% of patients, with severe pain

fulfilling the criteria of neuropathic pain accounting for 2-10% of these.[73] Despite many published studies in the medical literature regarding chronic post-surgical pain it is not a term which has been applied or adopted in the dental literature.

Other recognised pain conditions affecting the trigeminal system including atypical facial pain, atypical odontalgia, phantom tooth pain or idiopathic facial pain were excluded from this review although many of these patients may be experiencing pain that post-traumatic in nature, it is unclear using such diagnoses whether a causative relationship exists. In particular, it has been reported that patients diagnosed with atypical odontalgia undergo root canal treatment and/or extraction in an attempt to alleviate the pain, therefore it is not known whether the chronic pain is merely persisting despite the intervention or whether it is a product of the intervention. Furthermore, such chronic pains, that are those with an identifiable nerve injury component related to the onset of pain and those without an identifiable injury, may represent a continuum of the same condition.

The lack of consistency between studies in the terminology used for post-traumatic nerve injury in the trigeminal system and the reporting style of many studies as being present or absent without any further description or categorization of neuropathy makes it difficult to make comparisons or draw conclusions on the diagnostic criteria used for this condition.

Recommendations

Based on the best available evidence from this review, a basic chairside assessment of post-traumatic trigeminal nerve injury should include a minimum of the following diagnostic tests performed on the injured side and uninjured side for comparison. The patient should indicate whether sensation on the injured side is increased (hypersensitive), decreased (hyposensitive) or the same (normosensitive):

- Light touch sensation (ideally with Semmes Weinstein monofilaments, or cotton swab if unavailable
- Pinprick
- Cold sensation (metal spatula kept in iced water)
- VAS of subjective function

For the purpose of research, a more comprehensive testing protocol should be used, as suggested by The IASP Special Interest Group on Orofacial Pain (Table VII)[52]:

Comment [DM7]: A more detailed explanation o the testing protocol, methods and equipment used are included in Table VII.

For patients experiencing neurogenic discomfort or neuropathic pain as a result of trigeminal nerve injury, the NeuPSIG Diagnostic Grading[55] should be applied to include:

- Pain history, pain onset in relation to nerve injury, pain descriptors
- Neuroanatomical distribution of pain
- Confirmation of a lesion or surgical procedure in the affected nerve distribution
- Abnormal clinical neurosensory tests (as detailed above)

- Diagnostic imaging of the affected nerve (if clinically indicated)
- Assessment of functional and psychological factors as included in the DC/TMD[63]

CONCLUSIONS

This review highlights the poor level of evidence in this area. The considerable variation in the study characteristics, also reinforce the lack of consistency in applying diagnostic criteria, diagnostic tests and reporting outcomes of the assessment. There is an urgent requirement for a consensus in diagnostic criteria, criteria for assessment and outcome reporting between stakeholder organisations in order to progress knowledge in this field.

Comment [DM8]: This information is included earlier in the discussion section therefore is removed to avoid repetition.

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Figure 1. Flowchart of study inclusion

Figure 2. Proposed grading system for neuropathic pain (Finnerup et al 2016).

Table 1 Study Design and patient demographics

Study	Study design	Participants	Age	Gender (% F)	Mechanism of nerve injury	Division of trigeminal nerve affected		
						Maxillary	Mandibular	Both
Bagheri et al 2012	Retrospective CS	167	38.7	75	multiple		186	
Bagheri et al 2009	Retrospective CS	42	37.1	40	maxillofacial trauma	7	35	
Bagheri et al 2010	Retrospective CS	54	36.9	85	mandibular SSRO		54	
Bagheri et al 2010	Retrospective CS	222	31.1	77	multiple	0	222	
Benoliel et al 2005	Prospective CS	25	32.4	16	Zygomatic fracture	25	0	
Benoliel et al 2012	Prospective cohort	91	48.6	63	multiple	29	28	18
Calabria et al 2013	Prospective CS	14	25	64	BSSO		28	
D'Agostino et al 2010	Prospective CS	50	27	68	BSSO	0	100	
de Siqueira et al 2012	Prospective case control	19	47.94	74	oral surgery procedures	4	6	9
Elias LA et al 2014	Prospective CS	89	44.26	69	dental/surgical procedure		89	0
Essick et al 2007	RCT	184	25.1	71	Orthognathic surgery		184	
Gregg 1990	Retrospective CS	84	31	60	Multiple	6	78	
Walter & Gregg 1979	Retrospective CS	36	NR	NR	Orthognathic surgery		36	
Hillerup & Jensen 2006	Retrospective CS	52	47	67	Mandibular block analgesia		52	
Hillerup & Stoltze 2007	Retrospective CS	74	30	70	Previous third molar surgery		74	
Jääskeläinen K 2004	Prospective CS	20	32.8	60	BSSO		20	
Jaaskelainen SK et al 2005	Retrospective CS	58	40	76	Maxillofacial surgery		58	
Mundinger et al 2012	Retrospective CS	5	49	60	multiple		5	
Nkenke et al 2001	Prospective CS	23	44.6	61	Harvesting chin grafts		20	
Park & Kim 2010	Prospective CS	47	47.7	68	Implant placement		47	
Pitta et al 2001	Retrospective CS	5	34	83	Maxillofacial surgery		6	
Renton et al 2010	Retrospective CS	33	47.5	53	Mandibular injections		33	
Renton et al 2012	Prospective CS	120	36.7	68	Third molar surgery		120	
Sakavicius et al 2008	Retrospective CS	478	32.17	18	Trauma			478
Sandstedt & Sörensen 1995	Retrospective CS	226	38	68	Maxillofacial surgery		226	

Smith et al 2013	Retrospective CS	89	44.3	69	Maxillofacial surgery		89	
Zuniga et al 1998	RCT	130	37.1	65	Maxillofacial surgery		130	
Zuniga et al 2014	Retrospective CS	65	36	66	Maxillofacial surgery		65	

Table II. Neuropathic characteristics reported in the included studies

Neuropathic symptoms reported	IASP Definition	Number of studies reporting these symptoms
Anaesthesia	Absence of pain in response to stimulation which would normally be painful.	15
Hypoaesthesia	Decreased sensitivity to stimulation, excluding the special senses.	9
Paraesthesia	An abnormal sensation, whether spontaneous or evoked (not unpleasant)	11
Hyperaesthesia	Increased sensitivity to stimulation, excluding the special senses.	5
Hyperalgesia	Increased pain from a stimulus that normally provokes pain.	8
Hyperpathia	A painful syndrome characterized by an abnormally painful reaction to a stimulus, especially a repetitive stimulus, as well as an increased threshold.	2
Allodynia	Pain due to a stimulus that does not normally provoke pain.	10
Dysaesthesia	An unpleasant abnormal sensation, whether spontaneous or evoked.	12
Neuropathic pain	Pain caused by a lesion or disease of the somatosensory nervous system.	24

Table III. Diagnostic tests for neuropathy and neuropathic pain

Diagnostic tests for neuropathy	
Test	Number of studies using test
Clinical neurosensory tests*	24
Thermal Quantitative sensory testing	8
Electrical stimulation	3
Mental nerve blink reflex	3
Nerve conduction study	3
Diagnostic tests for neuropathic pain	
Patient self-report	28
Visual analogue scale	11
Questionnaire**	6
Diagnostic local anaesthetic block	4

* Clinical neurosensory tests included: light touch sensation, moving point direction, two-point discrimination, sharp –blunt discrimination, pinprick sensation, thermal sensation

**Questionnaires used: painDETECT, McGill pain questionnaire, Minnesota multiphasic personality index, Zung depression analysis, State trait anxiety index, Hospital anxiety and depression scale, Pain catastrophizing scale, Pain self-efficacy questionnaire, Oral health impact profile and others unspecified.

Table IV. Results / Outcome of diagnostic tests

Results / Outcome of diagnostic tests	Studies reporting this outcome
Frequency of neuropathic symptoms A variety of neuropathic terms were used including :anaesthesia, hypoaesthesia, paraesthesia, dysaesthesia, neuropathic pain, anaesthesia dolorosa, hyperalgesia or hyperpathia	Benoliel et al 2005 de Siqueira et al 2012 Gregg 1990 Walter & Gregg 1979 Hillerup & Jenson 2006 Hillerup & Stolze 2007 Jaaskelainen et al 2004 Jaaskelainen et al 2005 Mundinger et al 2012 Nkenke et al 2001 Pitta et al 2001 Renton et al 2010 Renton et al 2012 Sakavicius et al 2008 Sandstedt & Sorenson 1995
Classification of altered sensation (no alteration, negative (hypoaesthetic) sensations, mixed (negative + active) sensations or active (paraesthetic or dysaesthetic) sensations)	Essick et al 2007
Sensory impairment level (Normal, mild, moderate,severe,complete)	Zuniga et al 1998 Zuniga et al 2014
Deficit score (patient reported level of sensation with 10 denoting normal sensation)	Calabria et al 2013
Global sensitivity score (sum of scores on CNTs)	D'Agostino et al 2010
Functional sensory recovery (FSR) after surgical repair of nerve injury according to the medical research council scale (MRCS)	Bagheri et al 2012 Bagheri et al 2009 Bagheri et al 2010 Bagheri et al 2010
Classification of discomfort (absent, mild, mild-moderate, moderate, moderate-severe, severe)	D'Agostino et al 2010
Author's own diagnostic criteria for peripheral painful traumatic trigeminal neuropathy (PPTTN)*	Benoliel et al 2012
PainDETECT score (likely nociceptive pain, unclear, likely neuropathic pain)	Elias et al 2014

	Smith et al 2013
Effect of opioid or neuropathic pain medication on pain severity	Mundinger et al 2012 Park & Kim 2010
Frequency of functional problems associated with neuropathy	Renton et al 2010 Renton et al 2012 Sandstedt & Sorenson 1995 Smith et al 2013
Levels of anxiety, depression and catastrophizing associated with pain	Elias et al 2014 Smith et al 2013 Walter & Gregg 1979

Table V. Modified MRCS scale used by Bagheri et al.[12-15]

Grade	Description
S0	No sensation
S1	Deep cutaneous pain in autonomous zone
S2	Some superficial pain and touch
S2+	Superficial pain and touch plus hyperesthesia
S3*	Superficial pain and touch without hyperesthesia and static 2-point discrimination >15 mm
S3+*	Same as S3 with good stimulus localization and static 2-point discrimination of 7-15 mm
S4**	Same as S3 and static 2-point discrimination of 2-6 mm

*Indicates useful sensory function **Indicates complete sensory recovery

Table VI. Proposed diagnostic criteria for PPTTN (Adapted from Benoliel et al 2012)[8]

Diagnostic criteria	**Notes**
A Spontaneous or touch-evoked (stimulus dependent) pain predominantly affecting the receptive field of one or more divisions of the trigeminal nerve Duration ranges widely from episodic (minutes to days) and may also be constant.	Pain tends to spread with time and is mostly unilateral without crossing the midline. Paroxysmal pain patients may also have constant background pain. Time pattern may change over the course of the disease.
B Develops within 3 months of an identifiable traumatic event to the painful area or relevant innervation Continues for more than 3 months	Trauma, surgery, invasive dental treatment. *usually localised pain **Likely to cause dermatomal pain, may spread due to central mechanisms
C At least one clinically evident neurologic dysfunction: Positive sign 1. Hyperalgesia 2. Allodynia 3. Swelling or flushing And/or negative sign 1. Anesthesia 2. Hypoesthesia	Must be a constant feature and reproducible. Non-vital tooth is evidence of nerve damage. Clinical examination may be suitable. If area is amenable, quantitative sensory testing may reveal changes. Advanced neurophysiologic testing is not always available but certainly valuable, e.g., nerve conduction studies, electromyography, laser-evoked potentials, blink reflex, masseter inhibitory reflex. Convincing data from C may be considered sufficient.
D Imaging or neurophysiology demonstrating a neurologic lesion and its location	Imaging may often be historical, e.g., zygomatic fractures affecting the infraorbital nerve that have been decompressed, dental implants that impinged on nerve bundles but may have been removed. Root canal therapy is considered evidence of nerve damage. Neurophysiology (see above)
E Not attributed to another disorder	Other causes are ruled out by history, physical examination, and special investigations if necessary
Diagnostic level Fulfils criteria A,B and E Fulfils criteria A,B,C or D, and E Fulfils criteria A,B,C,D and E	 Possible neuropathic pain (NP) Probable NP Definite NP

Table 7. Proposed comprehensive test protocol adapted from Svensson et al 2011.[52] The initial quantitative sensory testing protocol was developed by the German Research Network on Neuropathic Pain (DFNS) and adapted for use in the orofacial region.[51] Tests should be carried out on the affected site and an appropriate control site for comparison. Images of the testing protocol can be found in a comprehensive review of somatosensory testing.[52]

Test	Description	Equipment
Cool detection threshold (CDT)	A small thermode applied to the affected nerve distribution is set at a baseline temperature and cools at a defined rate until the patient indicates when they first feel cold sensation. Test is repeated 3 times and an average value recorded.	Thermal QST apparatus
Warm detection threshold (WDT)	A small thermode applied to the affected nerve distribution is set at a baseline temperature and warms at a defined rate until the patient indicates when they first feel warm sensation. Test is repeated 3 times and an average value recorded.	Thermal QST apparatus
Thermal sensory limen (TSL)	The difference threshold for alternating cool and warm stimuli	Thermal QST apparatus
Cold pain threshold (CPT)	A small thermode applied to the affected nerve distribution is set at a baseline temperature and cools at a defined rate until the patient indicates when they first feel pain caused by cold sensation. Test is repeated 3 times and an average value recorded.	Thermal QST apparatus
Heat pain threshold (HPT)	A small thermode applied to the affected nerve distribution is set at a baseline temperature and warms at a defined rate until the patient indicates when they first feel pain caused by heat sensation. Test is repeated 3 times and an average value recorded.	Thermal QST apparatus
Mechanical detection threshold (MDT)	Semmes Weinstein monofilaments are placed perpendicular to the skin in the affected nerve distribution and force is applied until the filament deforms. At this point a known reproducible force is applied. An ascending and descending series of monofilaments applying different amounts of force is used to measure the contact detection threshold. This is repeated 5 times and a mean value taken.	Semmes Weinstein monofilaments
Mechanical pain threshold (MPT)	A custom-made weighted pinprick is applied to the affected nerve distribution. An ascending and descending series of pinpricks is used to measure the MPT. This is repeated 5 times and a mean value taken.	Weighted pinprick
Mechanical pain sensitivity (MPS) and dynamic mechanical allodynia (DMA)	MPS: Seven weighted pinprick stimuli of different intensities are applied in a random order and repeated five times for each test site. DMA involves moving innocuous stimuli such as a Q-tip, cotton wisp and soft toothbrush across the test site in between pinprick stimuli. The patient gives a numerical pain rating for each stimulus. A total of 50 stimuli (pinprick and tactile) should be given at each test site.	Weighted pinprick Q-tip Cotton wisp Soft toothbrush
Temporal summation of pain as wind up ration (WUR)	10 pinprick stimuli of equal intensity are given at an interstimulus interval of 1 Hz. The patient is asked to give a numerical pain rating for this stimulus which is compared to the pain rating for a single stimulus.	Weighted pinprick

	Each series of 10 stimuli is repeated 5 times in the affected nerve distribution and an average value is taken.	
Vibration detection threshold (VDT)	Vibrating tuning forks are placed over a bony prominence in the affected nerve distribution. The patient indicates if they can feel vibration or not and three series of descending stimulus intensities are used to determine the VDT.	Vibrating tuning forks
Pressure pain detection threshold (PPT)	A pressure algometer or pressure gauge device is applied to the affected nerve distribution. 3 series of slowly ascending stimulus intensities are applied and the patient indicates when pain is felt. An average value of the 3 readings is taken.	Pressure algometer or pressure gauge

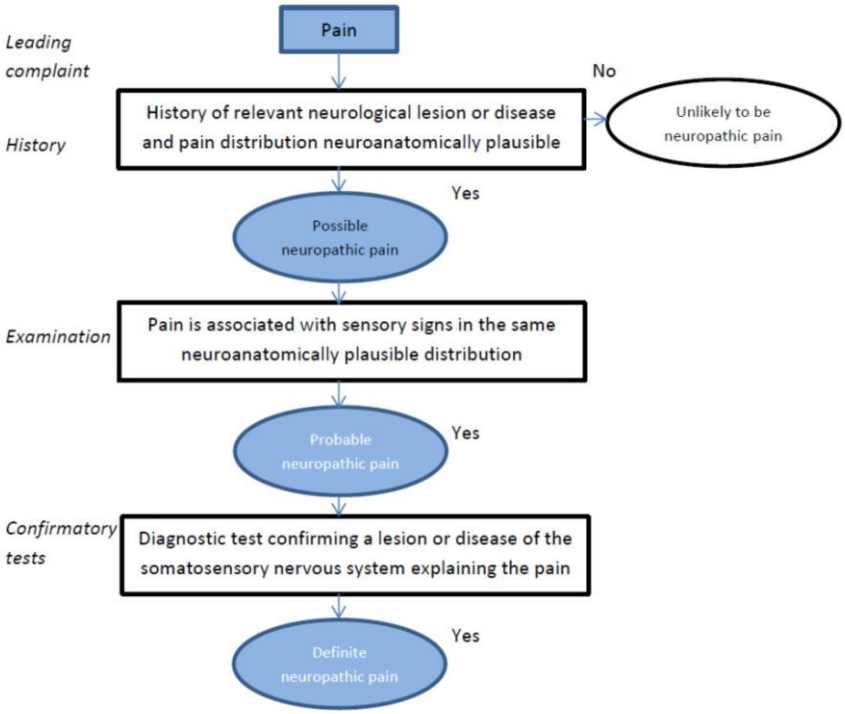

Figure 2. Proposed grading system for neuropathic pain (Finnerup et al 2016).

Figure 2.jpg

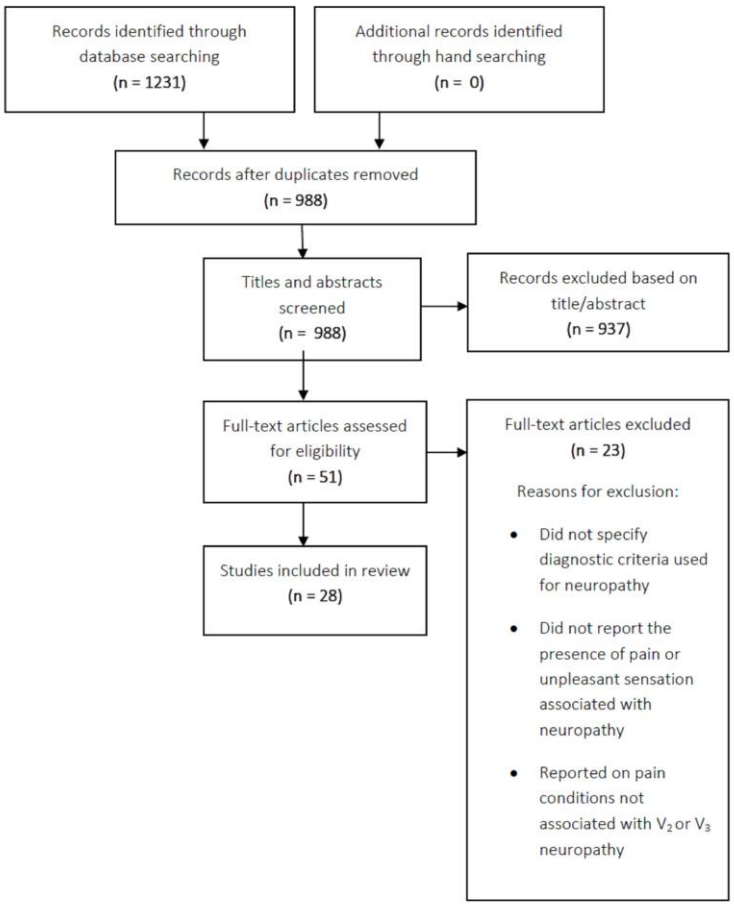

Figure 1. Flowchart of study inclusion

Figure1.jpg